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AMENDMENT

In the Specification:

At page 20, lines 19-25, please delete the paragraphs beginning with the text "**FIG. 7.**" and extending through the text "(SEQ ID NO:4)." and do not replace with any paragraph.

At page 20, line 27 to page 21, line 1 of the specification, please delete the existing paragraph and replace with the following paragraph, so that the text reads:

D1

FIG. 7. Mouse *ltbp-2* cDNA Clones. The schematic figure presents overlapping mouse cDNA clones representing the mouse *ltbp-2* coding sequence. A partial representation of the restriction sites is shown. A, *Avr*II; N, *Nae*I; Sa, *Sca*II; X, *Xho*I; B, *Bam*HI; C, *Cla*I; and E, *Eco*RI.

At page 21, lines 3-22 of the specification, please delete the existing three paragraphs and replace with the following three paragraphs, so that the text reads:

D2

FIG. 8A. *ltbp-2* Gene Expression in the Developing Mouse Skeleton. Shown is an overview of the of the *ltbp-2* gene during mouse development, as determine by tissue in situ hybridization. The figure presents an autoradiogram made by direct exposure of tissue sections to film after hybridization with radiolabeled probes, but before dipping slides in radiographic emulsion. Day 16.5 p.c. sections contain whole embryos sectioned in the mid-sagittal plane. Identical conditions were maintained throughout autoradiography and photography, making it possible to compare the overall strength of hybridization with antisense (top) and sense (bottom) probes. 1 cm = 20 mm.

FIG. 8B. *ltbp-2* Gene Expression in the Developing Mouse Skeleton. Shown is a selected brightfield microscopic view of mouse *ltbp-2* gene expression in cartilage of day 16.5 p.c. mouse embryos. Photograph was taken from tissue sections following a two week exposure to photographic emulsion. 1 cm = 20 mm.

D2 cont

FIG. 8C. *ltbp-2* Gene Expression in the Developing Mouse Skeleton. Shown is a selected darkfield microscopic view of mouse *ltbp-2* gene expression in cartilage of day 16.5 p.c. mouse embryos. Photograph was taken from tissue sections following a two week exposure to photographic emulsion. In all darkfield photographs red blood cell and other plasma membranes give a faint white signal that contributes to the background of the study. 1 cm = 20 mm.

At page 21, line 24 through page 22, line 15, please delete the entire paragraph beginning with "**FIG. 13.**" and extending through "40091 antiserum." and do not replace with any paragraph.

At page 62, line 18 to page 63, line 5 of the specification, please delete the existing paragraph and replace with the following paragraph, so that the text reads:

D3

In this study, the inventors isolated and characterized a novel murine fibrillin-like cDNA encoding LTBP-3. To clone the murine LTBP-3 gene, cDNA from a 3T3 cell cDNA library was amplified using human fibrillin-1 PCR™ primers under low stringency conditions (*i.e.*, annealing at 37°C initially for 10 cycles, followed by annealing at 60°C for 30 cycles). The results indicated that a murine DNA fragment of unexpectedly low homology (~50%) to human fibrillin-1 was obtained. Molecular cloning of the authentic murine fibrillin-1 transcript was also performed, confirming the human and murine fibrillin-1 coding sequences share >95% sequence

identity. The murine fibrillin-1 and PCR™ sequences were different, which suggested that the PCR™ product may have been derived from a related, fibrillin-like cDNA. The 3T3 cell cDNA library was screened at high stringency using the murine PCR™ product as the probe in order to test this hypothesis. A cDNA walking strategy eventually yielded seven overlapping cDNA clones (FIG. 1). It provides a unique mRNA of 4,314 nucleotides, with an open reading frame of 3,753 nucleotides (SEQ ID NO:3). The deduced molecule is a unique polypeptide of 1,251 amino acids (SEQ ID NO:4). Excluding the signal peptide (21 amino acids), the novel fibrillin-like molecule consists of five structurally distinct regions (Region 1- Region 5), and although similar to murine fibrillin-1 (FIG. 2A), its domain structure is unique as is evidenced by the schematic representation of LTBP-3 shown in FIG. 2B.

B3

At page 75, lines 7-11 of the specification, please delete the existing paragraph and replace with the following paragraph, so that the text reads:

In co-transfection studies of 293T Cells using pLTBP-3fl and pTGF-b1, immunoprecipitation of LTBP-3 and TGF-b1 was demonstrated by 293T cells following transient transfection and radiolabeling. Aliquots ($\sim10^6$ incorporated CPM) of radiolabeled media were immunoprecipitated and separated using 4%-18% gradient SDS-PAGE and either reducing or nonreducing conditions as described (Yin *et al.*, 1995).

B4

At page 75, line 21 to page 76, line 11 of the specification, please delete the existing paragraph and replace with the following paragraph, so that the text reads:

To identify new murine LTBP family members, independently designed degenerate oligonucleotide primers were synthesized based on a structural homology shared by human LTBP-1 and mouse LTBP-3 coding sequences: forward primer,

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5'-AAACGTCACACGTGAIACGTGAACGTTGCTTGCTGG-3' (SEQ ID NO:12); reverse primer, 5'-TTACGTCCACGTACACGTCTAGCAAGCAAGCA-3' (SEQ ID NO:13), and then used PCR™ to amplify single-stranded mouse embryo cDNA prepared from normal CD-1 mouse embryo mRNA. A band of approximately 400 basepairs (bp) was isolated and purified by agarose gel electrophoresis, the DNA was ligated into the TA cloning vector (InVitrogen), and the ligation mixture was used to transform competent bacteria. Plasmid DNA (from 28 colony forming units) was prepared and evaluated by DNA sequence analysis. As determined by sequence identity comparison, 16/28 plasmid DNAs coded for mouse LTBP-1, 11/28 coded for mouse LTBP-3, and 1/28 coded for an apparently unique sequence. The insert DNA from the unique plasmid was then used as a probe to screen a cDNA library prepared from 3T3 cells (Stratagene, Inc.). A walking strategy eventually yielded the overlapping cDNA clones shown in FIG. 7. Analysis of these clones identified an open reading frame of 5,430 base pairs. Comparison of sequence identity using the GAP and BESTFIT programs (Genetics Computer Group) revealed 79.7% identity between the mouse open reading frame and human LTBP-2 (Centrella *et al.*, 1991), but $\leq$ 47.1% identity between the mouse open reading frame and human LTBP-1 and mouse LTBP-3. The sequence comparison data agreed with chromosomal localization data, which collectively established that the sequence was the mouse homolog of human LTBP-2.

D5

At page 78, lines 24-25 of the specification, please delete the existing paragraph and replace with the following paragraph, so that the text reads:

The complete cDNA nucleotide sequence for murine LTBP-2 is shown in SEQ ID NO:1. The deduced amino acid sequence is shown in SEQ ID NO:2.

D6

At page 78, line 29 to page 79, line 27 of the specification, please delete the existing paragraph and replace with the following paragraph, so that the text reads:

The inventors have demonstrated that *ltbp-3* is widely and intensely expressed in both developing maternal tissues (*e.g.*, uterine decidua) and mouse embryo tissues (*e.g.*, mesenchyme, connective tissue, epithelia, and parenchyma). Tissue *in situ* hybridization was used to compare and contrast the developmental expression of *ltbp-2* and *ltbp-3*. FIG. 8A, FIG. 8B and FIG. 8C present an overview of *ltbp-2* expression in a mid-sagittal section of a mouse embryo at day 16.5 *p.c.* of development, when expression is strongest. The section was hybridized with a ^{35}S-labeled single stranded antisense riboprobe synthesized from a 580 base pair cDNA coding for the mouse LTBP-2 3' untranslated region. The probe showed <30% sequence identity with the 3' untranslated sequences of human *ltbp-1* and *ltbp-2*, which is too low to give spurious hybridization signals under our conditions. A ^{35}S-labeled single stranded normal sense riboprobe from the same cDNA construct was used as a negative control. *ltbp-2* expression above background was observed in the snout, base of the skull, tail, paw, lung, vertebrae, and large vessels of mouse embryos. Microscopy of day 16.5 *p.c.* embryo tissue sections, taken from the same slide used to prepare whole mount sections shown in FIG. 8A, demonstrated that the pattern of hybridization was due to significant *ltbp-2* gene expression by perichondrial and vascular wall cells. Positive signals were detected, for example, in perichondrial cells of cartilage aggregates located in the vertebral column (v), forelimb and tail, and at the base of the skull (FIG. 8B). Indeed, the perichondrium (pc) of all cartilage aggregates observed in these mouse embryo tissue sections was positively hybridized. *ltbp-2* was also expressed by vascular wall cells of the aorta (ao), and in blood vessels within lung parenchyma and within the connective tissue supporting hair follicle structures associated with the snout (s). In contrast, *ltbp-2* was expressed at insignificant levels (*i.e.*, below the experimental background) in the

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generalized mesenchyme/connective tissue, brain, peripheral nerve, tooth rudiment, lung epithelium, cardiac and skeletal muscle, gut epithelium, liver parenchyma, pancreas epithelium and islets of Langerhans, brown fat cells, and kidney parenchyma. These *in situ* hybridization results, which were reproduced using independent tissue sections, demonstrate for the first time that *ltbp-2* expression in developing mouse tissues is more restricted than that of *ltbp-3*.

D7

In the Claims:

Please amend claims 40, 43-46, 52-60, 62-64, 75, 76 and 78 so that the text of the amended claims read as follows:

40. (Thrice Amended) A method for binding a latent transforming growth factor β (TGF-β) protein in a sample, comprising contacting said sample with a purified mammalian LTBP-3 protein or polypeptide under conditions effective to allow binding of said LTBP-3 protein or polypeptide to said latent TGF-β protein; wherein said LTBP-3 protein or polypeptide specifically binds to latent TGF-β1 and exhibits at least 90% identity to the amino acid sequence of SEQ ID NO:4.

D8

43. (Twice Amended) The method of claim 40, wherein said sample is located within an animal and said LTBP-3 protein or polypeptide is administered to said animal in an amount effective to bind latent TGF-β in said animal.

D9

44. (Twice Amended) A method of binding latent TGF-β, comprising contacting a composition comprising latent TGF-β with a composition comprising a purified mammalian LTBP-3 protein or polypeptide in an amount effective to bind latent TGF-β; wherein said

LTBP-3 protein or polypeptide specifically binds to latent TGF-β1 and exhibits at least 90% identity to the amino acid sequence of SEQ ID NO:4.

45. (Twice Amended) The method of claim 44, wherein said composition comprising latent TGF-β is located within an animal and said composition comprising said LTBP-3 protein or polypeptide is administered to said animal in an amount effective to bind latent TGF-β in said animal.

D9 Cont

46. (Twice Amended) A method of binding latent TGF-β, comprising providing to an animal a composition comprising a purified mammalian LTBP-3 protein or polypeptide in an amount effective to bind latent TGF-β in said animal; wherein said LTBP-3 protein or polypeptide specifically binds to latent TGF-β1 and exhibits at least 90% identity to the amino acid sequence of SEQ ID NO:4.

52. (Twice Amended) The method of claim 46, wherein LTBP-3 binding to latent TGF-β regulates TGF-β activity in said animal.

D10

53. (Twice Amended) The method of claim 46, wherein LTBP-3 binding to latent TGF-β modulates the activation of TGF-β in said animal.

54. Twice Amended) The method of claim 46, wherein LTBP-3 binding to latent TGF-β modulates the activation of latent complexes that comprise TGF-β, thereby regulating TGF-β activity.

55. (Twice Amended) The method of claim 46, wherein LTBP-3 binding to latent TGF-β targets TGF-β to the extracellular matrix in said animal.

56. (Twice Amended) The method of claim 46, wherein LTBP-3 binding to latent TGF-β targets TGF-β to the bone matrix in said animal.

57. Twice Amended) The method of claim 46, wherein LTBP-3 binding to latent TGF-β targets TGF-β to connective tissues in said animal.

58. (Twice Amended) The method of claim 46, wherein LTBP-3 binding to latent TGF-β targets TGF-β to the cell surface of cells in said animal.

D10

59. (Twice Amended) The method of claim 46, wherein LTBP-3 binding to latent TGF-β protects latent TGF-β from proteolytic attack and activation in said animal.

60. (Twice Amended) The method of claim 46, wherein LTBP-3 binding to latent TGF-β protects latent TGF-β from proteolytic attack and activation during wound repair or tissue healing in said animal.

62. (Twice Amended) The method of claim 46, wherein said latent TGF-β is located within a tissue healing, wound repair tissue site or bone progenitor tissue site of said animal and wherein said LTBP-3 protein or polypeptide is provided to said tissue site.

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63. (Amended) The method of claim 62, wherein said latent TGF-β is located within a tissue healing or wound repair tissue site of said animal.

D12

64. (Amended) The method of claim 62, wherein said latent TGF-β is located within a bone progenitor tissue site of said animal.

75. (Twice Amended) A method of binding latent TGF-β within an extracellular matrix or connective tissue site of an animal, comprising contacting said tissue site with a purified mammalian LTBP-3 protein or polypeptide in an amount effective to bind latent TGF-β in said animal; wherein said LTBP-3 protein or polypeptide specifically binds to latent TGF-β1 and exhibits at least 90% identity to the amino acid sequence of SEQ ID NO:4.

D13

76. (Twice Amended) A method of binding latent TGF-β within a repair or bone progenitor tissue site of an animal, comprising contacting said tissue site with a purified mammalian LTBP-3 protein or polypeptide in an amount effective to bind latent TGF-β in said animal; wherein said LTBP-3 protein or polypeptide specifically binds to latent TGF-β1 and exhibits at least 90% identity to the amino acid sequence of SEQ ID NO:4.

78. (Twice Amended) A method of binding latent TGF-β, comprising administering to an animal a composition comprising a purified mammalian LTBP-3 protein or polypeptide in an amount effective to bind latent TGF-β in said animal; wherein said LTBP-3 protein or polypeptide binds latent TGF-β and comprises at least fifteen contiguous amino acids present in

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D14 SEQ ID NO:4 and exhibits at least 90% identity to the amino acid sequence set forth in SEQ ID NO:4.

Please add new claims 79-81, as follows:

79. (New) A method of binding a latent complex of TGF-β that comprises mature TGF-β and latency associated peptide (LAP), said method comprising contacting a composition comprising said latent complex of TGF-β with a composition comprising a purified mammalian LTBP-3 protein or polypeptide in an amount effective to bind to said latent complex of TGF-β; wherein said LTBP-3 protein or polypeptide specifically binds to latent TGF-β1 and exhibits at least 90% identity to the amino acid sequence of SEQ ID NO:4.

D15 80. (New) The method of claim 79, wherein said composition comprising said latent complex of TGF-β is located within an animal and said composition comprising said LTBP-3 protein or polypeptide is administered to said animal in an amount effective to bind to said latent complex of TGF-β in said animal.

81. (New) A method of binding a latent complex of TGF-β that comprises mature TGF-β and latency associated peptide (LAP), said method comprising providing to an animal a composition comprising a purified mammalian LTBP-3 protein or polypeptide in an amount effective to bind to LAP in a latent complex of TGF-β in said animal; wherein said LTBP-3 protein or polypeptide binds to LAP in said latent complex of TGF-β and exhibits at least 90% identity to the amino acid sequence of SEQ ID NO:4.